REMARKS

Favorable reconsideration is respectfully requested in view of the following remarks.

Applicants wish to express their appreciation to the Examiner for her courtesy and helpful suggestions provided the Applicants' undersigned representative during the telephone interview.

In the foregoing amendments, claims 61-62 are cancelled without prejudice and rewritten as independent claims 89-91.

Turning to the Official Action, claims 1-20 and 61-63 are rejected under 35 USC 103 as being unpatentable over Negoro et al. (USP 5,258,382) in view of Muller et al. (USP 5,858,410). This ground of rejection is respectfully traversed.

The inventors who are employees of the Assignee, Dainippon Pharmaceutical Co., Ltd., were the first to find that AS-3201 and related compounds. have an excellent aldose reductase inhibitor (usually referred to as "ARI") activity and are useful as a medicament for prevention or treatment of diabetic complications. They filed a patent application in the U.S.A. on June 19, 1992, which was granted as U.S. Patent 5,258,382. This U.S. patent is the cited Negoro et al. reference. Thus, the cited Negoro et al. patent is owned by the same Assignee as the present patent application.

Since then, the Assignee has made significant efforts for development of AS-3201 as a medicament in the U.S.A. Now, clinical tests of AS-3201 tablets have widely been performed in the U.S.A. and Canada with favorable results. For example, at the International Polyol Pathway Conference held in Kona, Hawaii on March 14-17, 2004, some clinical test results of AS-3201 were publicly presented by Dr. Bril, a professor of the University of Toronto and the Coordinating Investigator of the clinical study, and high praise was given by most of the attendants.

The attached Appendix I is a copy of the slides presented by Dr. Bril at the conference. As is seen from the slide copy, Dr. Bril concluded that "AS-3201 is a potent ARI". Dr. Bril used a very mild term "potent", but he might also have used the term "wonderful", because it is very rare for a speaker to announce the results of such clinical data favorably in such an international conference.

Great attention has been focused by the pharmaceutical industry on ARIs as a promising medicament for the treatment of diabetic complications in the U.S.A. However, to date there is no ARI approved as a medicament by the FDA. Under such circumstances, AS-3201 has been highly evaluated as potentially the first ARI to be approved. Thus it is respectfully submitted that such excellent properties of the present invention are unexpected from the prior art and are persuasive of nonobviousness.

As recognized by the Examiner, the Negoro et al. reference does not teach or suggest the unexpected benefits of using micronized AS-3201 in a solid dosage form according to the claimed invention. However the Examiner says that the effects of micronization of a compound are known by Muller et al. and hence, the present invention is obvious over the combination of Negoro et al. and Muller et al.

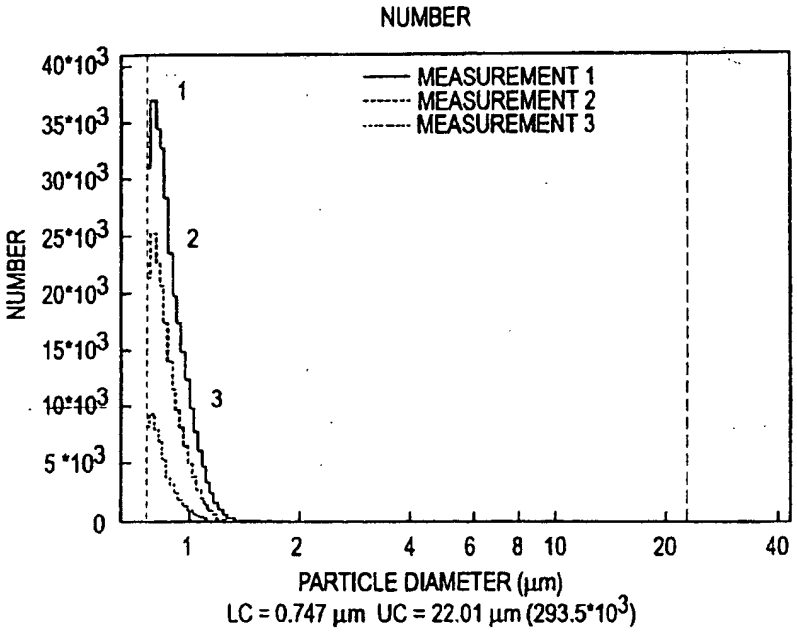
As discussed during the interview, Muller et al. is directed to a liquid nanosuspension of a difficult to dissolve drug for intravenous injection. Muller et al. teach away from using micron size drug particles because they would adversely effect the patient upon intravenous injection. See column 1, lines 52-65. In column 1, lines 26-30, Muller et al. teach that the average diameter of the particles is 10 nm to 1000 nm and that the proportion of microparticles in the particle population is very low. See also claim 1, which states that the proportion of particles greater than 5 microns is less than 0.1%. Muller et al. teach that the nanoparticles are preferably on the order of 200 to 600 nm. See Examples 1 to 4 in columns 11 and 12.

In Example 8 of Muller et al., the dissolution properties of nanoparticles are compared with microparticles. The results are shown in Fig. 9 and Fig. 10. With respect to the results of study in Example 8, it is mentioned "The decreasing area under the volume distribution curve is a measure of the dissolution of the nanosuspension."referring to Fig. 10 (cf. Muller et al., col. 14, lines 59-61). On the other hand, Muller teaches that the results "...shows the constant behaviour of the micronized particles in the same measurement medium."(cf. Muller et al., Fig. 9 and col. 14, lines 65-67).

Fig. 10 shows the dissolution properties of the nanosuspension, wherein the nanosuspension is diluted in several of hundred thousands folds and the numbers of solid

particles contained in the diluted nanosuspensions are measured, and the ordinates axis means the number of particles and the abscissae axis means the particle diameter (pm) as shown below.

Fig. 10



The data shown in Fig. 10 were obtained by measuring three times on each one sample at a fixed interval (start of measurement at times : T=0 s, T =450 s, T =1,100 s), wherein the numbers "1", "2" and "3" means the times of measurement. As is seen in Fig. 10, the area under the volume distribution curve is decreasing in the order of 1 → 2 →3. That is, the total volume of the whole particles was 121,000 um^3 at the 1st measurement, and was 83,762 μm^3 at the 2nd measurement, and was 42,038 μm^3 at the 3rd measurement (cf. Muller et al., col. 14, lines 56-59). Thus, in case of the nanosuspensions, a large portion of the solid particles disappeared, i.e. dissolved, with lapse of time.

Muller et al. teach at col. 14, lines 49-61 as follows (emphasis added by Applicants):

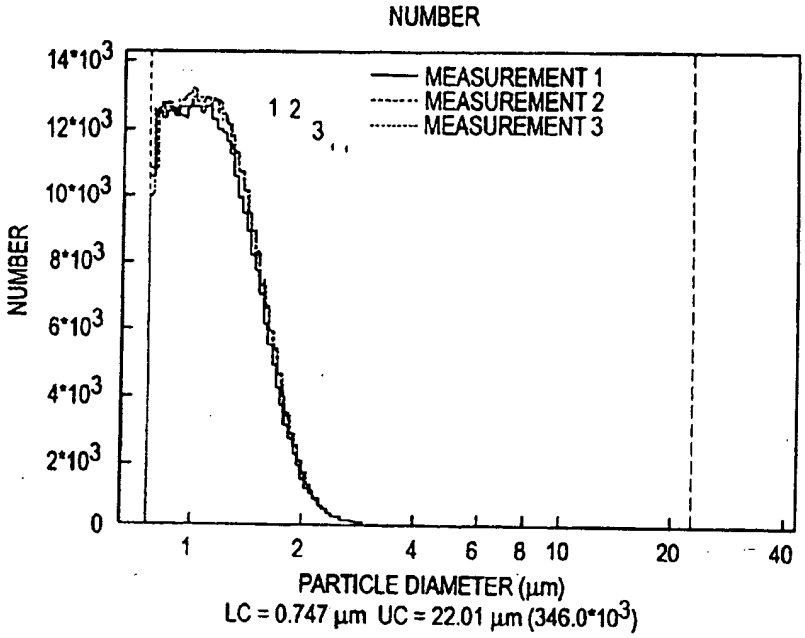
"Measurement of the nanosuspension, i.e. particles in the nanometer size, led - in spite of 0.9% NaCl solution saturated with drug - to dissolution of the particles within the measurement time of approx. 10 min, 65% of the particles dissolving. The Coulter counter volume distribution of the nanosuspension at the three successive measurements (start of measurement at times: T=0 s, T =450 s, T =1,100 s, duration of one measurement: 150 s) gives a total volume of the particles of 121,000 μm^3 during the first measurement, 83,762 μm^3 during the second measurement and a value of 42,038 μm^3 during the third measurement (Fig. 10). The decreasing area under the volume distribution curve is a measure of the dissolution of the nanosuspension."

The underlined data "65% of the particles dissolving" is calculated in the following manner:

The difference in the total volume between the 1st data and 3rd data
(= dissolution amount) = 121,000 - 42,038 = 78,962 μm^3,
Then, the rate of dissolving amount = (78,962/121,000) X 100 = 65%.

It should be noted that this "65% dissolution" is of nanoparticles. In the case of microparticles, different results were obtained as shown in Fig. 9 as follows:

Fig. 9



That is, as seen from the above Fig. 9, in case of microparticles, no dissolution was observed.

With respect to this different result, Muller et al. mentioned as follows (cf. col. 14, lines 37-48) (emphasis added by Applicant):

> "Introduction of RMKP 22 drug particles which had been ground in an air jet, i.e. particles with a diameter of 3.64 µm into this 0.9% NaC1 solution saturated with drug accordingly led to no solution phenomena at all within the measurement time of approx. 10 minutes (three repeat measurements of 150 s at intervals of 100 s), the three measurement curves obtained in succession being congruent (Fig. 9). The total volume of the particles of a sample is 393,000 μm^3 during the first measurement, 391,400 μm^3 during the second measurement and then 386,500 μm^3 (Fig. 9).
> The total volume of the particles remains constant over the period of the measurement cycle."

Thus, Muller et al. disclose:

(i) In the case of nanoparticles, a dissolution phenomenon was observed (Fig. 10), but

(ii) In the case of microparticles, no dissolution phenomenon was observed (Fig. 9).

Muller et al. does contain a general discussion of the Noyes-Whitney law.

The Examiner says in the Office Action, page 5, line 5 from the bottom to page 6, line 2 as follows (emphasis added by Applicants):

> "Applicant's arguments have been fully considered but they are not persuasive. The examiner points out that Muller also recognizes that sparingly soluble drugs have a problem with low bioavailability and that the bioavailability is increased with <u>better solubility of the active, thus the Noyes-Whitney law is applied</u>. Therefore, applicant's argument of unexpected bioavailability is expected as taught by Muller et al. One would be motivated to look to Muller's guidance since Negoro's active is also sparingly soluble and one would expect similar problems."

From the passages underlined in the above, it is assumed that the Examiner's understanding with respect to Noyes-Whitney law is as follows:

"Noyes-Whitney law is concerned with solubility."

When the results of Fig 9 are understood on the basis of the Examiner's understanding of Noyes-Whitney law, the data of Fig. 9 (the data of microparticles) do not conform to Noyes-Whitney law.

That is, according to the Examiner's understanding with respect to Noyes-Whitney law,

(1) the nanoparticles conform to Noyes-Whitney law (Fig. 10), but

(2) the microparticles do not conform to Noyes-Whitney law (Fig. 9).

It is further mentioned in Muller et al., col. 1, lines 38-49 as follows (emphasis and parenthetic phrases added by Applicant):

> "The preparation of medicament particles having a size in the nanometer range has many advantages from the pharmaceutical technology, biopharmaceutical, pharmacological and medical aspect. ("A")
> Some of these are:
> 1. The dissolution rate increases as the particle surface area increases in accordance with the Noyes-Whitney law. ("B"). As a result, the rate of flooding of active compounds increases, and the maximum plasma level is reached faster (e.g. oral or i.v. administration of a nanosuspension). The preparation of nanosuspensions is therefore of interest for all substances with which the dissolution rate is the determining factor for the bioavailability."

In the above, the passage underlined and marked as "B" is a discussion about the properties of nanoparticles, and not microparticles. This is clear from the discussion which is underlined and marked "A" above it. This will be well understandable from the fact that Noyes Whitney law is not applied to microparticles, in other words that Muller et al. teaches that the microparticles tested did not conform to the Noyes Whitney law.

Moreover, the teachings of the Noyes Whitney law relate to the solubility of particles themselves. The Noyes Whitney law, and the teachings of Muller et al., have nothing to do with the unexpected discovery of the present invention, that the micronization of AS-3201 provides a pharmaceutical composition in solid dosage form to dissolve quickly. The Examples of the specification teach the preparation of tablets containing AS-3201. See Examples 1 and 2 and Comparative Example 1 on pages 10 and 11. The tablets of Examples 1 and 2 contained micronized particles of AS-3201 having a mean particle size of 1.5 and 10 microns, respectively. In contrast, the tablets of Comparative Example 1 contained particles of AS-3201 having a mean particle size of microns. The tablets were dissolved by the Paddle method recited in the claims as described on pages 11-12 of the specification.

The results are shown in Figure 1. The tablets of Comparative Example 1 had a dissolution percentage of only about 10% within 15 minutes. On the other hand, the tablets of Example 2 had a dissolution rate of about 65% within 15 minutes. Moreover, the tablets of Example 1 had a dissolution percentage of about 90% within 15 minutes. Thus, the use of micronized AS-3201 in the claimed range resulted in an unexpected and remarkably improved dissolution rate of the tablet containing the micronized AS-3201. This remarkably fast dissolution rate of the tablet could not have been expected or obvious from the teachings of Negoro et al. or Muller et al. or the Noyes Whitney law.

Regarding the issue of particle size, claim 1 of Muller et al. defines the nanoparticles as follows:

(i) to have an average diameter of 10nm~1000nm (= 0.01 ~ 1μm),

(ii) the proportion of particles larger than 5μm in the total population being less than 0.1 %, and

(iii) prepared by pulverizing with a specific device, i.e. a piston-gap homogenizer.

Further, it is disclosed in Muller et al., at col.1, lines 26-31, that the proportion of microparticles in the particle population in Muller et al. invention is very low as follows:

"The average diameter of the dispersed phase is between 10 nm and 1,000 nm (determined by photon correlation spectroscopy), the distribution of the population being quite narrow, that is to say the proportion of microparticles in the particle population is very low."

Thus, the nanoparticles used in Muller et al. are defined very strictly with respect to the particle size.

The reason why the particle size is defined so strictly is that the nanosuspension shall be administered intravenously. That is, when the particles have larger than nanometer range, there is a possibility of the particles to block the vein when administered intravenously. Thus, the nanoparticles in Muller et al. cannot be replaced by microparticles as defined in the present invention.

The Examiner pointed out in the Office Action, page 3, lines 7-12 as follows:

"One would be motivated to do so since Muller et al. disclose that an increased surface area through reduction of particle size allows for a faster rate of dissolution. Although Muller teaches the range of 0.01 to 1 micron and instant range is "in a

range above 1 micron", it is deemed obvious to a skilled artisan to manipulate and tweak the prior art's particle range to obtain optimum results thorough routine experimentation."

However, according to the facts shown in Fig. 9 and Fig. 10, that is, the facts that nanoparticles showed dissolution phenomenon but microparticles did not, there is no motivation in the reference to use the particle size of the claimed invention.

It should further be noted that the average particle size defined in Muller et al. is essentially different from the average particle size (mean particle size) as defined in the present invention. The nanoparticles used in Muller et al. have an average particle size of 10nm~1000nm (= 0.01~1 μm) and contain the particles larger than 5 μm being less than 0.1 %. As mentioned above, the nanoparticles shall not contain the particles having particle size larger than 5 μm. The reason why the nanoparticles shall not contain such larger size particles is mentioned in col. 1, line 60-62 as follows:

"As a nanosuspension, the active compound can be injected without blockade of blood capillaries."

And hence, when the particles contain those having a particle size larger than 5 μm, the particles shall be subjected to centrifugation to remove such large particles (cf. Muller et al., col. 13, line 17-46 (Example 6) & Fig. 7). That is, as shown in Fig. 7, when Sample A containing particles larger than 5 μm was subjected to centrifugation at 1559 gravity for 30 minutes, Sample B was obtained, and said Sample A was subjected to centrifugation at 3056 gravity for 30 minutes, Sample C was obtained, by which procedure the proportion of the particles having a particle size larger than 5 μm can be reduced.

On the other hand, the microparticles of the present invention have a mean (average) particle size of in a range of above 1 μm to less than about 20 μm, which may contain nanoparticles but contain much amount of microparticles. Accordingly, even if a suspension is prepared with the micronized AS-3201 of the present invention, it cannot be administered intravenously because it would induce blockade of blood capillaries.

It is further indicated by the Examiner in the Office Action, page 3, line 4 from the bottom to page 4, line 5 as follows:

"Applicant argues that amended claims are outside of Muller's range of 0.01 to 1 micron. It is argued that the saturation solubility taught in Muller et al pertains to the nanometer range and not the micrometer range. Applicant's arguments have been fully considered but they are not persuasive . Muller et al. teach a range of 0.01 to 1 micron and applicant merely recites "above 1 micron" which falls under an obvious scope and parameter of the prior art. For instance, 1.001 is above 1 micron, however it is still an obvious parameter to a skilled artisan thorough routine optimization. Therefore, the amendment does not overcome the prior art's range rejected over obviousness."

Such position is respectfully traversed because it overlooks the concept of "mean particle size". Unless specified otherwise, in both of the present invention and in Muller et al., the particle size is defined by "mean (average) particle size". The term "mean particle size" in the present invention is used in the same meaning as the term "average diameter" in Muller et al. When the particles have a "mean particle size" of 1 um, it means that the particles consist of 50 % of particles having a particle size of less than 1 μm and 50 % of particles having a particle size of 1 μm or more. However, as is pointed out above, when half of the particles are particles having a particle size of micron order, even though the remaining half thereof is those having a particle size of nano-order, such particles are not included in the nanosuspension intended by Muller et al. in view of the definition in nanoparticles in Muller et al. That is, even if the claimed composition contained particles having a mean particle size of 1.001 microns, this means that 50% of the particles would have a particle size below 1.001 micron, and 50% of the particles would have a size above 1.001 micron. Such a large amount of microparticles could not be administered intravenously and would be contrary to the teachings of Muller et al.

Thus, it is respectfully submitted that the teachings of Muller et al. will rather support the unobviousness of the present invention.

Regarding the issue of Muller's disclosure as to solid particle, it is disclosed in Example 1 of Muller et al. that a coarsely dispersed suspension is prepared along with the following "Basic recipe" containing a medicament RMKP22 and pharmaceutically acceptable additives such as Tween 80, and

the suspension is charged into Micron LAB 40 and homogenized in 4 cycles to prepare a nanosuspension containing particles having an average particle size of 208 nm.

Basic recipe:
RMKP 22 3.0
Tween 80 0.1
Aqua dest. to 100.0

In Examples 2 to 5, 9, 13 to 16, nanosuspensions are prepared in the same manner as described in Example 1, by homogenizing the main active ingredient together with the pharmaceutically acceptable additives such as Glycerol 85%, Mannitol, CMC-Na, Lecithin S 75, Pluronic F68, Tween80. The pharmaceutically acceptable additives used therein may have a function to stabilize or prevent undesirable aggregation of the solid nanoparticles of active compound contained in the suspension, and hence will be essential components for the desired nanosuspensions.

The Examiner pointed out in the Office Action, page 5, lines 9 to 12 as follows:

"Applicant's arguments have been fully considered but they are not persuasive. The examiner points out that Muller et al teach nanosuspensions. Suspensions are solid particles suspended in an immiscible liquid, thus Muller does in fact teach solid particles."

However, in all examples disclosed in Muller et al., the products are all suspensions but not a "solid dosage form" *per se* according to the claims. The final products of Muller et al. are all a suspension containing pharmaceutically acceptable additives in addition to the nanoparticles active compound.

The products of Muller et al. are subjected to the test for "Long-time stability of nanosuspensions" in Example 9; "Stability of nanosuspensions during sterilization autoclaving A121" in Example 10; "Stability of nanosuspensions during sterilization: gamma sterilization" in Example 11; "Stability of nanosuspensions during sterilization as a function of the surfactant concentration" in Example 12, and these tests should be for checking whether those products have the desired properties as the final pharmaceutical product. Thus, all products in the working examples are concerned with a

nanosuspension which will be as a final pharmaceutical product which is intravenously administered to a patient.

The active compound contained in the suspensions is solid, but there is no specific teaching in Muller et al. that the solid particles are isolated. With respect to this matter, there is only a description in Muller et al., col. 1, lines 32-35 as follows:

> "The nanosuspension can also be lyophilized or spray dried, and the nanoparticles of a nanosuspension can also be incorporated into a solid carrier matrix."

However, there is no specific disclosure that the nanoparticles are isolated by using the lyophilization or spray drying.

Moreover, there remain various problems to be solved, such as whether the isolated microparticles keep in the form of nanoparticles. It is further questionable how to separate the pharmaceutically acceptable additives such as mannitol, surfactants, glycerol, etc.

These subjects would not easily be solved by any person skilled in the art. For example, the results of Example 10 shown in Fig. 13, indicate that a suspension of "A1+2 AUTOCLAVED" showed less suspension stability than "PARENT SUSPENSION A". That is, when the suspensions were sterilized in an autoclave under the conditions of pressure; 2 bar, temperature; 121°C, period of time; 15 minutes, the number of particles having larger particle size (> 5 μm) in the "A1+2 AUTOCLAVED" product much increased than that of "PARENT SUSPENSION A". On this point, it is mentioned in Muller et al., col. 15, lines 52-54 as follows;

> "The number of particles greater than 5 μm rose as a result of exposure of the nanosuspensions to heat and the resulting formation of aggregates."

In view of the description, there is no assurance that the nanoparticles do not aggregate to change into microparticles during the lyophilization or spray drying procedure.

However, a person skilled in the art would never have tried but rather avoided to isolate the solid particles from the nanosuspension in Muller et al., because it is contrary to common sense and further it is costly to destroy the completed nanosuspension and to isolate the solid particles therefrom.

It will be rather usual to prepare directly the desired nanoparticles instead of taking the step of preparation of a nanosuspension.

Even if any person dares to try to isolate from the once completed nanosuspension, it will be difficult as mentioned above, and it will be not obvious to a person skilled in the art.

Thus, the teachings of Muller et al. do not motivate one skilled in the art to prepare a solid dosage form according to the present invention.

Regarding the combination of Negoro et al with Muller et al., the primary reference of Negoro et al. reference discloses AS-3201 *per se*, but does never teach or even suggest to pulverize it for obtaining the microparticles of the present invention.

On the other hand, the teachings of Muller et al. are as explained above, which are summarized below:

(i) As the results of the study of dissolution properties of nanosuspension in comparison with microparticles in Example 8 of Muller et al., the dissolution phenomenon, "65% dissolution" was observed in nanosuspension (Fig. 10), but was not observed in microparticles.

According to the Examiner's understanding of Noyes-Whitney law as relating to solubility, the Noyes-Whitney law might be applied to nanoparticles, but not to microparticles.

(ii) The nanoparticles mentioned in Muller et al have an average particle size of 10nm to 1000nm and contain particles having a diameter larger than 5 μm in less than 0.1 % and further are prepared by using a specific device: a piston-gap homogenizer. Thus, the microparticles of the present invention are never overlapping with the nanosuspension of Muller et al. in terms of the particle sizes.

(iii) Muller et al. merely teach nanosuspension but not solid particles per se contrary to the Examiner's comments. That is, Muller et al. disclose the preparation of nanosuspension, but not isolation of solid particles therefrom.

(iv) Neither reference alone or in combination suggest that the solid dosage form tablets of the claimed invention will have remarkably improved dissolution percentage by using micronized particles of AS-3201 having the claimed size range.

In summary, it is respectfully submitted that there is no motivation to combine the teachings of Muller et al. with Negoro et al. Moreover even if the teachings are combined, it is respectfully submitted that the claimed invention is not suggested by the combined teachings of Negoro et al. with Muller et al.

Claims 1-20 and 63-82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Negoro et al (5,258,382) in view of Arbuthnot et al (6,458,811).

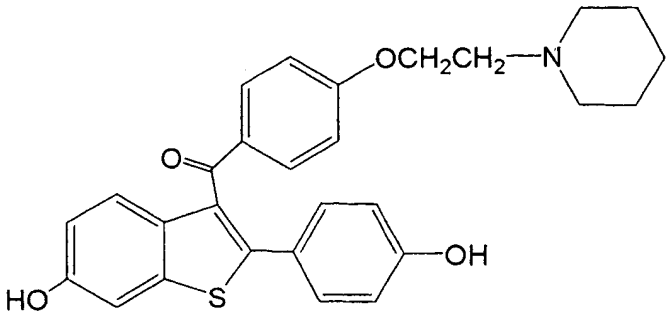
As mentioned above, the primary Negoro et al. reference do not teach the micronized AS-3201. The Arbuthnot et al. reference does not teach or even suggest the microparticles of the present invention, nor does the Arbuthnot et al. give any motivation to combine its teachings with Negoro et al.

The Examiner points out in the Office Action, page 7, lines 6-7 as follows:

> "Arbuthnot et al. teach a benzothiophene compound in particulate form with a mean particle size between 5 and about 20 microns. See column 2, lines 66-67."

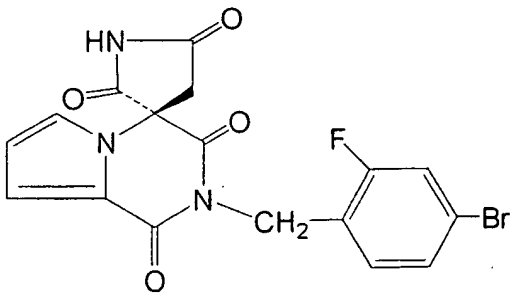
The benzothiophene is known as an osteoporosis alleviating agent having the general name of "Raloxifene" and having a chemical structure as shown below. "Raloxifene" has a solubility in water of about 0.3 mg/ml at 25°C. (cf. Arbuthnot et al., col. 24, line 29)

Chemical structure of Raloxifene



On the other hand, AS-3201 of the present invention has a chemical formula as shown below and has an aldose reductase inhibitory activity and is useful as a medicament for the prevention and/or treatment of diabetic complications. Besides, AS-3201 has a solubility in water of 0.0111 mg/ml at 25°C. In a Declaration of Mr. Sanjoba as mentioned hereinafter, it is mentioned that AS-3201 has a solubility in water of <0.05 mg/ml at 25°C, but this was data obtained in 1994, and thereafter, the solubility has been re-examined and corrected to the above.

Chemical Structure of AS-3201



Raloxifene disclosed in the cited Arbuthnot et al. and AS-3201 of the present invention are clearly different in physicochemical properties as well as in chemical structure.

For example, Raloxifene has a solubility in water of about 27 times higher than that of AS-3201 of the present invention (= 0.3/0.0111).

Further, Raloxifene has the solubility in other solvents as summarized in the following table, which is prepared based on the disclosure of Arbuthnot et al., col. 24, lines 28-32:

Solubility of the Raloxifene hydrochloride

Solvents/°C / pH	Solubility (mg/mL)
Simulate Gastric Fluid USP at 37°C /pH 1.2*1)	0.003
Water at 25°C /pH about 6*2)	0.3
Simulate Intestinal Fluid USP at 37°C /pH 6.8*1)	0.002

*1) These pH values are defined in U.S. Pharmacopoeia.

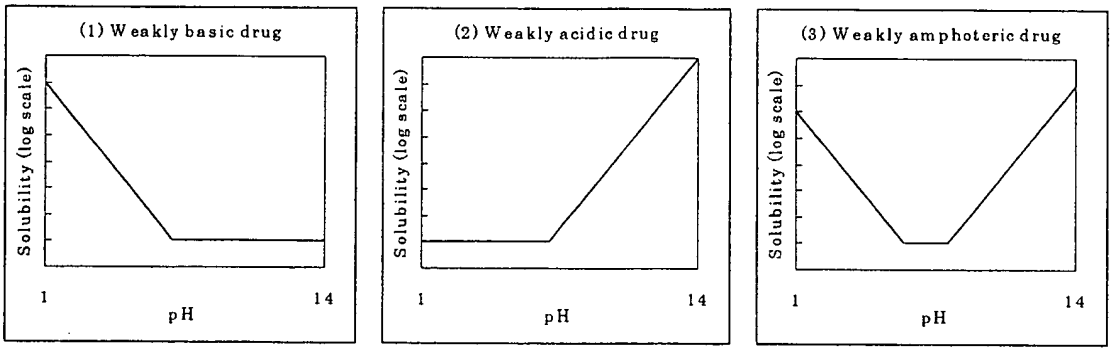
*2) pH about 6 : estimate (distilled water has usually about pH 6 because it usually absorbs CO_2)

Raloxifene hydrochloride has a high solubility in water. The solubility in Simulate Intestinal Fluid USP is less than 1/100 of the solubility in water. It is known that many of drugs are an organic electrolyte with weakly acidic and/or basic dissociated substituents and that the solubility of these drugs may vary depending on pH values with the following rules (1) to (3):

(1) A weakly basic drug having weakly basic dissociated substituent has a higher solubility at a lower pH value, and the solubility will decrease with increase of pH value.

(2) A weakly acidic drug having weakly acidic dissociated substituent has a lower solubility at a lower pH value, and the solubility will increase with increase of pH value.

(3) Weakly amphoteric drug has the lowest solubility at around neutral pH value.



The AS-3201 of the present invention has a higher solubility at a higher pH value, and hence is classified into the (2) group. On the other hand, Raloxifene hydrochloride is classified into the (3) group from the chemical structure, nevertheless it has a highest solubility in water at about pH 6 and shows extremely lower solubility in both of higher and lower pH values. Such a unique aqueous solubility of Raloxifene would never be expected by a person skilled in the art. Accordingly, the Arbuthnot et al. reference disclosing a compound having such very unique properties does not give any motivation to the artisan along the lines of the present invention.

The Examiner points out in the Office Action, page 7, line 8 from the bottom and seq. as follows:

> "Arbuthnot states that compounds with poor solubility can have their bioavailability enhanced by increasing the surface area of the particles. Further, Arbuthnot states that the aqueous solubility of a drug potentially impacts the dissolution rate of the solid dosage form since the dosage form and the active are exposed to the gastrointestinal tract. Thus, the two related physical properties of drugs, the surface area and particle size, can alter the dissolution rate of the dosage form. The impact of surface area, which is a function of particle size is illustrated by the Noyes-Whitney law. See column 24, lines 25-55."

However, it is taught in Arbuthnot et al., col. 22, lines 36-55 that the milling is not always practical or desirable and that the milling does not necessarily give the best results. Thus, such a teaching of Arbuthnot et al. does not give any motivation to the artisan to arrive at the claimed invention.

The Examiner further indicates various points as to Noyes Whitney law referring to Arbuthnot et al. in the Office Action. So, it is explained below how Raloxifene does not conform to Noyes-Whitney law by referring to the data shown in Tables 6-8 of Arbuthnot et al., col. 25, line 1 to col. 26, line 20.

In TABLE 6, the factors of "Milling Technology", "Surface Area, m^2/gm", "Mean Particle Size (μm)" are shown for four bulks; Bulk Lot # 1 ~ Bulk Lot #4. In TABLE 8, the factors of "%Dissolved at 10 Minutes", "%Dissolved at 30 Minutes" of those four bulks are shown. Those factors of TABLE 6 and TABLE 8 are summarized in the following table.

	Bulk Lot #	1	2	3	4
Table 6	Milling Technology	Micronized	Recrystallized	Ball Milled	Slurry Milled
	Surface Area (m^2/gm)	6.09	2.28	2.10	0.45
	Mean Particle Size (μm)	3.9	8.4	23.3	48.1
Table 8	% Dissolved at 10 Minutes	50	41	31	15
	% Dissolved at 30 Minutes	78	68	55	35

From the data shown in the above table, the following points may be derived.

In comparison of the data of Bulk Lot # 2 & 3,

(1) the "Surface area (m^2/gm)" in both bulks are almost same (2.28 vs 2.10) .

(2) however, the "% Dissolved at 10 or 30 minutes" in both bulks are different (41 vs 31 or 68 vs 55).

These facts, which were experimentally confirmed, cannot be explained by the Noyes-Whitney law. That is, when both particles have the same Surface area, then they shall also be the same as in "%

Dissolved at 10 or 30 minutes" in view of Noyes-Whitney law, but the data obtained by the experiment do not conform to the law.

Accordingly, the Noyes-Whitney law can not be applied at least to Raloxifene.

It should be noted that the Noyes-Whitney law does not apply to every kind of compound.

As mentioned on page 6 of the Applicants' response dated April 4, 2003:

"Please refer to "Design and Evaluation of Peroral Pharmaceutical Preparation (in Japanese)", edited by Mitsuru Hashida, Yakugyo Jihosya, February 10, 1995, pp.81-84, 168-171 (cited in the International Search Report of the original PCT/JP98/04658) thereof (which was submitted as Supplemental Information Disclosure Statement on September 26, 2000). An English translation of this publication is submitted concurrently herewith.

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However, this publication also discloses the following opposite teachings:

(A) However, in practice, pulverization alone cannot always elevate the dissolution rate. (cf. English translation of pp.81-84 at page 3, lines 11-12)

(B) However the size should be of the submicron level or less for a great influence of size reduction to be exerted on solubility, and therefore pulverization usually made on many drugs may not be very effective in increasing the solubility by size reduction. (cf. English translation of pp. 168-171 at page 1, lines 14-17)

(C) However, in some cases, the finer the particle is, the more easily flocculation occurs, causing reduction of the surface area in contact with water (effective surface area), and thus the dissolution rate of some drugs is even decreased by pulverization. In particular. hvdrophobic drugs are very apt to flocculate. As shown in Fig 7-2, the dissolution rate of pulverized griseofulvin is slower than that of non-pulverized griseofulvin. (cf. English translation of pp. 168-171 at page 1, lines 8-3 from the bottom)"

Thus, Noyes-Whitney law is not applicable to every kind of drug. The Noyes-Whitney law was introduced in around 1904, and hence, if the Noyes-Whitney law is applicable to every kind of drug, the inventions of Muller et al., Arbuthnot et al. (USP 6,458,811) and others would be obvious and would never been granted.

Then, can the Noyes-Whitney law be applied to AS-3201 of the present invention.

In the above item (C), it is mentioned as follows:

"In particular, hydrophobic drugs are very apt to flocculate. As shown in Fig. 7-2, the dissolution rate of pulverized griseofulvin is slower than that of non-pulverized griseofulvin."

The above indicates that a hydrophobic drug does not conform to Noyes-Whitney law. According, if AS-3201 is a hydrophobic drug, then it will be clear that AS-3201 does not conform to Noyes-Whitney law.

Enclosed please find a Declaration by Mr. Sanjoba. In the Declaration, the solubility and partition coefficient of AS-3201 have been studied and it is indicated that AS-3201 has the following properties.

(i) It is practically insoluble in water.

(ii) It is very soluble in dimethyl sulfoxide, acetone, and acetonitrile, but is sparingly soluble or slightly soluble in ethanol, chloroform, and n-octanol.

(iii) As is assumed from those solubility characteristics, and as is confirmed by exact measurement, it has a high partition coefficient (P) value (= 74).

By the way, it is known that hydrophobic compounds are well soluble in n-octanol and hence have a large log P, but hydrophilic compounds are well dissolved in water and have a smaller log P.

Based on the above solubilities in various solvents and partition coefficient (P) value, it can be concluded that AS-3201 is a hydrophobic drug. Accordingly, one skilled in the art would have understood that the Noyes-Whitney law could not be or might hardly be applied to AS-3201.

Thus, the teaching of Arbuthnot et al. do not give any motivation to the artisan to arrive at the present invention.

Regarding the combination of Negoro et al. with Arbuthnot et al., Negoro et al. disclose AS-3201 *per se* but not about the particle size thereof nor micronization thereof.

On the other hand, the teaching of Arbuthnot et al. is as summarized below:

(i) Raloxifene disclosed in Arbuthnot et al is clearly distinguished from AS-3201 of the present invention not only in chemical structure but also in various properties such as physicochemical properties, pharmacological activities. Moreover, Raloxifene has unique solubility characteristics in that it has the largest solubility at about pH 6 and shows extremely low solubility at lower or higher pH region.

(ii) Raloxifene does not conform to Noyes-Whitney law. NoyesWhitney law is not necessarily applied to any kind of drug.

On the other hand, AS-3201 of the present invention is a hydrophobic drug and hence, it does not conform to Noyes-Whitney law.

In view of the above, the claimed invention is neither taught nor suggested by the combined teachings of Negoro et al. and Arbuthnot et al.

Claims 61-62 are further rejected under 35 U.S.C. 103(a) as being unpatentable over Negoro et al (5,258,382) in view of Muller et al (5,858,410) or Arbuthnot et al (6,458,811) in further view of Schneider et al (5,356,636). This ground of rejection is also respectfully traversed.

Claims 61 and 62 (now presented as new claims 89 to 91) are concerned with a fast-dissolving pharmaceutical composition in a solid dosage form, further comprising a specific stabilizer in addition to the micronized AS-3201 as claimed in claim 1.

As mentioned above, the primary Negoro et al. reference do not teach the micronized AS-3201, and further the secondary Muller et al. and Arbuthnot et al. references do not teach or even suggest the microparticles of the present invention. Those cited references do not teach or even suggest such a composition as claimed in claims 61 and 62 (new claims 89 to 91). The further cited Schneider et al reference (5,356,636) do not give any motivation to combine its teachings with Negoro et al. as is explained below.

The Examiner points out in the Office Action, page 9, lines 6-8 as follows:

"Schneider et al teach the use of stabilizers or antioxidants when the active agent is sensitive to oxidation. Stabilizer such as the instant acids of claims 61 and 62 are taught on column 4, line 68."

It is disclosed in Schneider et al, col. 4, line 63 to col. 5, line 4 as shown below. "It is particularly important when the dry powders are used as animal feed additives in the case of active substances which are sensitive to oxidation to add antioxidants such as ethoxyquin, butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA) or tocopherol, and stabilizers such as citric acid, phosphoric acid or phytic acid and their alkali metal or alkaline earth metal salts, or else complexing agents such as ethylenediaminetetraacetic acid (EDTA) or nitrilotriacetic acid (NTA)."

Such a disclosure of Schneider et al will never teach the stability of the composition of the present invention.

Even after the chemical structure of AS-3201 is known, it will be not readily understand whether AS-3201 is stable or not, and further it will be not predictable how the AS-3201-containing composition can be stabilized, because it has never been known the reason why it is unstable, due to decomposition by oxygen (oxidization)? due to decomposition by moisture? or any other causes?

When a person skilled in the art sees the chemical structure of AS-3201 of the present invention, can he/she predict whether it is sensitive to oxidation?

Only after completion of the present invention could it be understood whether the technology as taught by Schneider et al might be applicable or not. Even though the technique as disclosed in Schneider et al. is applicable to the present invention, it is respectfully submitted to be based upon hindsight.

It shall further be noted that the invention of Schneider et al. is concerned with stabilization of "dry powders which are insoluble in hot water and which contain one or more fat-soluble vitamins and/or one or more carotenoids," as defined in claim 1. Thus, the drugs to be stabilized are more fat-soluble vitamins and/or one or more carotenoids. It is absolutely not clear from the disclosure of

Schneider et al. that among the plural of drugs which one may be or shall be stabilized by stabilizers such as citric acid, which drug is sensitive to oxidation. Thus, the teaching of Schneider et al. is vague from the technical viewpoint.

As already pointed out in the Applicants' Response filed on April 4, 2003 on page 10, lines 8-5 from the bottom:

> "On the other hand, in the present invention, the specific acidic substance has an acidity more potent than that of AS-3201 and is incorporated for the purpose of prevention of hydrolysis of the active substance due to the moisture absorption during storage, which is clearly distinguished from the cited Schneider et al."

The cause of instability is clearly different between the drugs in Schneider et al. and AS-3201 of the present invention, the former being due to oxidation but the latter being hydrolysis.

Even if any person skilled in the art would have noted that AS-3201 is easily hydrolyzable, there is no reasonable reason whether said skilled person will have interest to the disclosure of Schneider et al. concerning a technique of anti-oxidation.

Thus, Schneider et al. never gives any motivation to the artisan to arrive at the present invention.

Regarding the combination of Schneider et al. with other three references, Negoro et al. disclose AS-3201 *per se* but do not about stabilization thereof.

Muller et al. mention about dispersion stabilization of suspension which is not of stabilization of the active ingredient. On this point, as already explained in the response dated April 4, 2003 at page 10, lines 7 to 12:

> "Firstly, although in Muller et al., dispersion-stabilizing substances and charge stabilizers are also incorporated in order to prevent aggregation of the particles as shown in claims 12-15 and claims 1618, which are effective for prevention of aggregation of particles in the suspension. These substances used in

Muller et al. are essentially different from the stabilizer (i.e. acidic substance such as citric acid, tartaric acid, maleic acid, malic acid) of the present invention in both kinds and in the object and effect of use thereof."

Arbuthnot et al. disclose a formulation of Raloxifene which is entirely different from AS-3201 of the present invention and do never teach or even suggest stabilization of AS-320 1.

Further, as is pointed above, the teaching of Schneider et al. is mere hind-sight and further is entirely different stabilization technique from that of the present invention.

Accordingly, even if Schneider et al. reference is combined to other Negoro et al., Muller et al. and Arbuthnot et al. references, while there is no reasonable reason to combine them, still the present invention as claimed in new claims 89 to 91 is not obvious over these references and is well patentable over them.

In summary, it is respectfully submitted that all grounds of rejection have been overcome, and that the application is now in condition for allowance. Such allowance is solicited.

Respectfully submitted,

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